Chronology of Significant Activities Undertaken During the Applicable Regulatory Period

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
X		09/30/95	Initial IND submission including protocols 1165/24,34,42,43,46	
X		10/23/95	CMC correction & clarification of BPS lots used in toxicology studies	
X		10/25/95	Clarification of finished product impurities limits	
X		10/26/95	Correction of finished product capsule shell colours	
X		10/27/95	Submission of pre-final report 1165/40 (mutagenicity test)	
X		11/02/95	Submission of Phase II protocol 251/95/01	
X		11/03/95	Temperature stability conditions for VML 251 tablets	
X		12/26/95	CMC - Newly discovered BPS impurities	
X		01/12/96	Correction to amendment 008	
X		03/13/96	New CMC - tablet blister packs & Protocol 251/95/02	
X		03/18/96	Request for review of carcinogenicity study 1165/45	
X		04/11/96	Protocol amendment to 251/95/02 - New dose and more patients	
X		04/12/96	Request for review of study 261/96/02	
X		05/14/96	Protocol amendment to 251/95/02 - New investigators	
X		06/21/96	Toxicology and clinical update: Vol 1 : Reports for 1165/12,35,36,40,41 Vol 2 : Report for 1165/11 Vol 3 : Reports for 1165/31,38 Vols 4-6 : Report for 1165/24 Vols 7-8 : Report for 1165/34 Vols 9-10 : Report for 1165/42 Vols 11-12 : Report for 1165/43	
X		06/25/96	Protocol amendment to 251/95/02 - New investigators	
X		07/02/96	Protocol amendment to 251/95/02 - More patients	
X		08/08/96	Request for review of study 251/96/10	
X		08/29/96	IND Safety report - Adverse effect from study 251/96/03	
X		09/20/96	Request for end of Phase II meeting	

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
X		09/30/96	Questions reguarding pharmacokinetic studies for Phase III	
X		11/22/96	Annual report	
X		12/16/96	Information addendum to annual report	
X		01/22/97	New protocol 251/96/14	
X		02/21/97	Request for CMC meeting	
X		03/11/97	Protocol amendment to 251/96/14 - New dose & Protocols 251/96/06,07,08,10	
X		03/21/97	Protocol amendment to 251/96/14 - New investigator	
X		03/31/97	Response to CMC questions re: amendments 010 and 021	
X		04/08/97	End of Phase II CMC pre-meeting package	
X		04/11/97	Attachment to amendment 027	
X		04/16/97	Protocol amendment to 251/96/06,07,08 - New investigators	
X		04/21/97	Draft toxicology reports 1165/32,80	
X		04/30/97	Protocol amendment to 251/96/06,07,08 - New investigators	
X		05/19/97	Protocol amendment to 251/96/06,07,08 - New investigators	
X		05/27/97	Protocol amendment to 251/96/06,07,08 - New investigators	
X		06/04/97	End of Phase II meeting minutes	
X		06/05/97	Protocol amendment to 251/96/06,07,08 - New investigators	
X		06/09/97	CMC meeting minutes	
X		06/16/97	Protocol amendment to 251/96/06,07,08 - New investigators	
X		06/20/97	Transfer of Agent	
X		07/14/97	Protocol amendment - New investigators	
X		07/17/97	General correspondence	
X		08/11/97	Protocol amendment - New investigators	
X		08/11/97	General correspondence	
X		08/22/97	Protocol amendment - New investigators	
X		09/09/97	General correspondence	
X		09/10/97	Information amendment: Clinical	
X		09/16/97	General correspondence	
X		10/13/97	General correspondence	
X		10/30/97	Comments on protocols VML 251/96/14, 06, 07 and 08	
X		10/31/97	General correspondence	

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
X		11/28/97	General Correspondence (Pharmacokinetic & metabolism data)	
X		12/03/97	General Correspondence (CAD protocol)	
X		12/08/97	Annual Report We only have vols. 9-12 these are on the shelf Blue Binders	
X		12/08/97	Annual Report (12 volumes)	
X		12/31/97	New Protocol Blue Binders	
X		01/02/98	New Protocol VML 251/97/04	
X		01/06/98	New Protocol Blue Binders	
X		01/06/98	New Protocol VML 251/97/03	
X		01/28/98	General Correspondence Blue Binders	
X		01/28/98	Protocol Amendment Blue Binders	
X		01/28/98	Annual Report Blue Binders	
X		01/28/98	General Correspondence	
X		01/28/98	Protocol Amendment	
X		02/13/98	Protocol Amendment New Investigator Blue Binders	
X		02/17/98	Protocol Amendment	
X		03/02/98	Protocol Amendment Blue Binders	
X		03/03/98	Protocol Amendment	
X		03/17/98	Protocol Amendment New Investigator Blue Binders	
X		03/17/98	Protocol Amendment : New Investigator	
X		03/26/98	General Correspondence Blue Binders	
X		03/26/98	General Correspondence	
X		04/07/98	Protocol Amendment New Investigator Blue Binders	
X		04/07/98	Protocol Amendment : New Investigators	
X		05/06/98	Protocol Amendment Change in Protocol Blue Binders	
X		05/07/98	Other: Pre-Meeting Request Blue Binders	
X		05/07/98	Protocol Amendment : VML251/97/04 and VML251/96/08	

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
X		05/07/98	Pre-NDA Meeting Request	
X		05/27/98	Protocol Amendment Blue Binders	
X		05/27/98	Protocol Amendment : A Randomized, Double-Blind Placebo-Controlled Multi-center Study to Assess the Efficacy and Cardiovascular Safety of VML 251 in Patients with Known and at a High Risk of Coronary Artery Disease Treating An Acut Attack of Migraine"	
X		06/03/98	Pre-NDA	Background package
X		06/03/98	Pre-NDA Background Blue Binders	
X		06/03/98	Background package for Pre-NDA Meeting	
X		06/10/98	Pre-NDA	FDA contact report
X		07/01/98	Pre-NDA	Final pre-NDA meeting minutes and overheads
X		07/09/98	General Correspondence Updated 1571 Blue Binders	
X		07/09/98	General Correspondence	
X		07/24/98	Admin. Change in FDA Form 1572 Blue Binders	
X		07/24/98	Administrative Change in FDA Form 1572	
X		08/06/98	Request for Pre-NDA (CMC) Meeting Minutes Blue Binders	
X		08/06/98	Request for Pre-NDA (CMC) Meeting	
X		08/25/98	General Correspondence Pre-NDA Meeting Minutes Blue Binders	
X		08/25/98	General Correspondence : Pre NDA Meeting Minutes	
X		08/28/98	Pre-NDA	CMC Meeting Briefing package
X		08/28/98	Pre-NDA CMC Meeting Briefing Pack Blue Binders	
X		08/28/98	General Correspondence : Pre NDA (CMC) Meeting Briefing Package	
X		09/17/98	General Correspondence Pre-NDA (CMC) Meeting Agenda Blue Binders	
X		09/17/98	Other: Revised Investigators Brochure Blue Binders	

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
X		09/17/98	Other: Administrative Change in FDA 1572 Blue Binders	
X		09/17/98	General Correspondence : Pre NDA (CMC) Meeting Agenda	
X		09/17/98	Other : Revised Investigator's Brochure	
X		09/17/98	Other : Administrative Change in FDA Form	
X		09/17/98	Protocol Amendment : New Protocol	
X		09/22/98	Protocol Amendment New Protocol Blue Binders	
X		09/24/98	Client Correspondence	Statement on a non-proprietary name adopted by the USAN Council: frovatriptan succinate
X		11/10/98	Protocol Amendment New Investigators 2 vols Blue Binders	
X		11/10/98	Protocol Amendment : New Investigator	
X		01/19/99	General Correspondence Pre-NDA (CMC) Meeting Minutes Blue Binders	
X		01/19/99	General Correspondence : Pre-NDA CMC Meeting Minutes	
	X	01/29/99	Original NDA Submission	
X		01/29/99	Annual Report	
	X	02/12/99	Amendment to a Pending Application	Revised volume of clinical references; pdf files for nonclinical reports; additional 15 desk copies of Volume 1.001 and Volume 1.002
	X	02/25/99	Amendment to a Pending Application	Correction to the Annotated Package Insert and Provision of Additional Electronic Reviewer's Aids
	X	03/09/99	General Correspondence	Frovatriptan NDA follow-up
	X	03/24/99	FDA Letter	Acknowledgement of NDA Submission; Notation of the primary and secondary user fee target dates
	X	03/26/99	General Correspondence	Desk copy for Lana Chen of selected Clinical documents
	X	04/01/99	General Correspondence	Response to Request from Dr. Stolzenberg
	X	04/21/99	General Correspondence	Copy to R. Katz of the Response to Documentation Request from the Division of Scientific Investigation request

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
	X	04/21/99	Response to Documentation Request	Provision of Clinical Trial information to the Division of Scientific Investigations
X		05/10/99	Protocol Amendment Change in Investigator(s) Blue Binders	
X		05/10/99	Protocol Amendment : Change in Investigators	
	X	05/12/99	Fax from FDA	Minutes from the Executive CAC Meeting of April 27, 1999
	X	05/15/99	Fax to FDA	List of Sponsor Attendees for the April 28, 1999 teleconference (Re-faxed on June 30, 1999 at FDA Request)
	X	05/19/99	General Correspondence	Proposed new name of MIDURA
	X	05/20/99	General Correspondence	Initial response to Executive CAC meeting minutes and proposed full CAC meeting date in late June
	X	06/08/99	Amendment to a Pending Application – Amendment #4	CMC Information
	X	06/11/99	Section 9 – 120-day Safety Update	• Pharmacology study conducted in conscious dogs, entitled, "Comparative effects of two 5-$HT_{1b/1d}$ receptor agonists, frovatriptan and sumatriptan, on carotid and coronary arteries in conscious dogs." (Report No. VML 251 RP 16-01) • Addendum to report of the long-term open-label safety study (251/96/08) containing data on the 50 patients who were ongoing at the time of the original NDA submission. • Data from the first three months of the ongoing 6 month open-label safety study (251/98/08) • number of patients in the study • number of migraines attacks treated • number of doses • AEs up to 3 months for all patients or until study discontinuation for patients who left the study prior to 3 months
	X	07/08/99	General Correspondence	Briefing Document for July 29, 1999 CAC Meeting
	X	07/12/99	Client Correspondence	Copy of Briefing document to be subject of meeting on July 29, 1999 with FDA

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
	X	07/23/99	Fax from FDA	Full CAC questions prepared by the Neuropharm Division
	X	08/04/99	Fax from Dr. Powell to Dr. Stolzenberg of FDA	Follow-up to post-CAC meeting (July 29, 1999)
	X	08/13/99	Fax from FDA	Response from Labeling and Nomenclature Committee on Midura name
	X	08/24/99	Fax from FDA	FDA minutes of the full CAC Meeting of July 29, 1999
	X	08/26/99	Fax from FDA	Revised FDA minutes from the full CAC meeting of July 29, 1999
	X	08/30/99	General Correspondence	Request for teleconference to discuss proposed studies in response to CAC meeting/briefing documentation.
	X	09/17/99	Fax to FDA General Correspondence	Follow-up to Teleconference of August 31, 1999
	X	09/17/99	General Correspondence	Provision of Sponsor minutes of the full CAC meeting
	X	09/22/99	General Correspondence	Draft timeline for frovatriptan NDA
	X	09/28/99	Fax to FDA	Copies of References noted in the September 17, 1999 Submission
	X	09/29/99	General Correspondence	Hard copy of September 28, 1999 fax and Additional PK information
	X	09/29/99	CMC Information	Response to FDA letter of July 2, 1999
	X	10/01/99	General Correspondence	Follow-up to August 31, 1999 teleconference and letter of September 17, 1999. Presentation of the timing of submission of new data and request for a teleconference to clarify the impact on NDA review and action target date.
	X	10/04/99	FDA Teleconference Minutes	Minutes of FDA teleconference on Aug 31, 1999
	X	10/08/99	Fax from FDA	PK data requests and list of attendees at Oct 7, 1999 teleconference
	X	10/13/99	Human Pharmacokinetics and Bioavailability Amendment	Provision of Report 1165/212-D0142 (renal impairment)
	X	10/14/99	Client Correspondence	Fax to Dr. Katz regarding whether mouse carcinogenictiy study would have been acceptable were it not for findings in the chromosome aberration assay
	X	10/18/99	Letter to Dr. Katz	Presentation of preliminary data from the investigative toxicology study

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
	X	10/19/99	Client Correspondence	Copy of teleconference report between Mary Prendergrast of Elan and Russell Katz
	X	10/21/99	Fax to FDA	Response to Questions raised by FDA Biopharmaceutics Reviewer on 21-Sept-99
	X	10/21/99	Human Pharmacokinetics and Bioavailability Amendment	Response to Questions raised by FDA Biopharmaceutics Reviewer on 21-Sept-99
	X	11/02/99	Letter to Drs. Temple and Katz	Statement of assessment of the NDA by Roger Brimblecombe, CEO of Vanguard Medica Limited
	X	11/30/99	Fax from FDA	Letter containing additional CMC questions/clarifications
	X	12/13/99	Fax to FDA	CMC requests
	X	12/13/99	Desk Copy	Request for FDA opinion of p53+/- mice study
	X	12/30/99	General Correspondence	Copies of e-mail communications concerning the p53 mouse study
	X	12/30/99	Human Pharmacokinetics and Bioavailability Amendment	Dissolution data
	X	01/21/00	Fax from FDA	Minutes of Executive CAC meeting on Jan 18, 2000
	X	01/21/00	Nonclinical and Clinical Update	Major amendment containing results of rat dose range finding as well as discussion of the nonclinical and clinical packages. Intent was to extend the review clock.
	X	01/28/00	CMC update	Response to November 30 letter on CMC deficiencies; also methods validation package was included.
	X	02/03/00	CMC update correction	Corrections received from sponsor incorporated into the January 27 update; complete set provided for the field copy.
	X	02/10/00	General Correspondence	Response to CAC minutes
	X	02/18/00	Client Correspondence	Dissolution data for the FDA Reviewer
	X	02/21/00	General Correspondence	Provision of dissolution data from all time points for all batches
	X	02/22/00	Human PK update	Provision of dissolution data from all time points for all batches
	X	02/22/00	Nonclinical update	Provision of final lymphoyte report (draft included in January 21 amendment)
	X	02/28/00	CMC update	Corrected Methods Validation package
	X	03/06/00	Nonclinical update	Hard copy of TK tables sent previously by e-mail to Dr. Stolzenberg

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
	X	03/06/00	Letter from FDA	"Approvable Letter"
	X	03/09/00	Nonclinical update	Provision of final reports for Studies 7070-101 and 1165/201
	X	03/21/00	General Correspondence	Executive CAC minutes from March 14, 2000
	X	03/23/00	General Correspondence	Letter of appreciation for the teleconference to disclose the results of the Executive CAC meeting
X		03/28/00	Annual Report for 99	
	X	04/05/00	General Correspondence	Response to minutes of CAC executive committee
	X	04/10/00	Fax to FDA	NDA Method Validation Letter
	X	04/10/00	Response to Request for Information	Provision of a copy of the List of Investigators
	X	04/13/00	General Correspondence	Regulations referenced, response to CAC minutes, prior response to CAC meeting
	X	04/14/00	General Correspondence	Claim for Exclusivity
	X	04/14/00	CMC response	Provision of samples
	X	04/21/00	Fax from FDA	Receipt of sample materials for method validation testing
	X	04/21/00	General Correspondence sent by fax as well	Additional response to the minutes of CAC executive committee, specifically in regard to the p53 mouse study.
	X	04/28/00	Fax from FDA	Approvable Letter - Acknowledgement of receipt of submissions, issues to be addressed for approval
	X	05/03/00	General Correspondence	Notification of the intent to file an amendment to the NDA following receipt of the April28, 2000 approvable letter
	X	06/06/00	General Correspondence	Notification of sponsor name change from Vanguard to Vernalis
	X	06/27/00	Nonclinical Update	Initial results from the in vivo portion of the p53 study
	X	06/27/00	Nonclinical Update	Submission of p53 study amendments
	X	07/05/00	Clinical Update	Submission of Request for Partial Pediatric Waiver
	X	07/18/00	General Correspondence	Request for Review of Tradenames
	X	08/21/00	Clinical Update	Response to approvable letter including the 2nd safety update 17 vols
	X	08/23/00	Nonclinical Update	Submission of telephone report for DeGeorge teleconference of August 9, 2000 in re: p53 study

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
	X	08/24/00	CMC Update	Response to CMC issues in approvable letter
	X	09/08/00	Electronic Review Aid for Clin Upd. Submitted 8/21/00	Sent PDF files (Postscript files sent by mistake on 8/21/00) (no separate copy of this submission kept)
	X	09/15/00	Clinical Update	Submission of Pediatric Plan
	X	09/18/00	Nonclinical Update	Submission of Draft p53 study Report
	X	09/26/00	Letter from FDA	Acknowledgement of receipt of correspondence to NDA notifying FDA of sponsor change
	X	10/02/00	Clinical Update	Provision of proposed pediatric study request
	X	10/03/00	CMC Update	Withdrawal of August 24 response and submission of response to CMC issues in approvable letter
	X	10/03/00	Nonclinical Update (3 volumes)	Submission of final p53 report as response to approvable letter
	X	10/03/00	Labeling Update	Submission of revised PI in response to approvable letter – final response; contains cross-reference to all approvable letter responses
	X	10/23/00	Letter from Dr. Katz	Acknowledgement of receipt of submission to NDA for proposed labeling
	X	10/27/00	CMC Update	Response to reviewer request for documents
	X	11/02/00	Fax to FDA	Request for Executive CAC meeting minutes on Oct 31, 2000 and minutes of teleconference on Nov 1, 2000
	X	11/06/00	Fax to FDA (CMC Update)	Address to send field copies of CMC documents/information
	X	11/08/00	Nonclinical Update	Follow-up to teleconference with Division Staff on Nov 1, 2000
	X	11/08/00	Fax from FDA	Minutes of two Agency meetings regarding NDA
	X	11/16/00	Correspondence	Response to minutes of teleconference of Nov 1, 2000
	X	11/16/00	Clinical Update	Reviewer request for datasets for studies, VML 251/96/08 and VML 251/98/08
	X	11/17/00	Letter from Dr. Katz	Minutes of meeting of Executive Carcinogenicity Committee on Oct 31, 2000
	X	11/17/00	Letter from Dr. Katz	Minutes of meeting between Quintiles, Vernalis, Elan, and FDA on Nov 1, 2000 to discuss results of Executive CAC meeting

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
	X	11/22/00	Nonclinical Update	Response to minutes of Executive CAC Meeting October 31, 2000
	X	12/06/00	Fax from FDA	Two letters that contain Agency comment on proposed pediatric written request and proposed pediatric development plan
	X	12/07/00	Letter from FDA	Name change to Vernalis
X		12/07/00	Change in contact for U.S. Agent and Notification of Change of Sponsor Name (change to Jim Bustrack)	
X		12/07/00	General Correspondence: Request for Review of and Comments on Planned Clinical Protocol	
	X	12/12/00	General Correspondence	List of Vernalis/Elan/Quintiles participants in Dec 13 teleconference
X		01/10/01	Protocol Amendment: New Protocol – VML 251/00/01 and Investigator Information	
	X	01/29/01	Letter from Quintiles	Change of named IND contact
X		01/29/01	Change in contact for U.S. Agent and Notification of Change of Sponsor Name (change to Mary Beatty)	
	X	02/01/01	General Correspondence	Change in ownership of this application (change from Vernalis to Elan)
	X	02/02/01	Letter from Elan to FDA	Transfer of NDA
	X	02/12/01	Telecon report between Jackie Ware and Syd Gilman	Introduction
	X	02/14/01	Telcon with Syd Gilman and J Ware	Communications re p53 etc
X		03/06/01	Protocol Amendment: New Investigators	
X		04/13/01	Protocol Amendment: Changes to Protocol	
X		04/16/01	Protocol Amendment: New Protocol, New Investigator (Protocol 251/00/02)	
	X	05/07/01	Response to Approvable letter	Part A and B 4 vols
X		05/07/01	IND Annual Report (2 November 99 thru 1 November 2000)	
	X	05/17/01	Telecon with Lana Chen	Confirmation of receipt
	X	05/24/01	Telcon with Lana Chen	Clarification of response
X		05/25/01	Protocol Amendment: Changes to Protocol	
	X	06/21/01	Voicemail	Requesting information
X		06/24/01	Letter from FDA with CMC review comments	

IND 48,933	NDA 21-006	DATE	DESCRIPTION OF AMENDMENT/SUBMISSION/ CORRESPONDENCE/ACTIVITY	COMMENTS
X		07/20/01	Protocol Amendment: New Investigators	
	X	08/03/01	Response document to clinical questions	Response to clinical request for CRF's (request came by Email)
	X	09/07/01	Response to CMC reviewers comments	Emails exchanged between June and September
	X	09/20/01	FDA nonclinical questions	E Mail from FDA with non-clinical question
X		09/20/01	Protocol Amendment: Changes to Protocol and New Investigators (251/00/02)	
X		09/24/01	Information Amendment: Chemistry/Microbiology (Diosynth submission)	
	X	09/26/01	E mail sent to FDA	Response to nonclinical data request of 9/24/01
	X	09/27/01	Amendment to FDA	Response to nonclinical data request of 9/24/01
	X	10/18/01	Secure email from Lana Chen	Courtesy Copy (unsigned) f Exec-CAC minutes
	X	10/23/01	Secure email to FDA	Questions for Exec-CAC and inquiry to complete labeling review
	X	10/23/01	Secure email from Lana Chen	Labeling questions on Pregnancy Category C
	X	10/25/01	Secure email to Lana Chen	Response to labeling questions, dated 10/23/01
	X	10/25/01	Secure email from Armando Olivia	FDA's proposed label for Frovatriptan
	X	10/26/01	Amendment to FDA	Nonclinical Labeling response to questions received in 10/23/01
	X	11/08/01	Secure email from Lana Chen	Carcinogenicity Assessment Committee Minutes of October 02, 2001
	X	11/08/01	Secure email from Lana Chen	FROVA Approval Letter
X		11/19/01	Protocol Amendment: Changes to Protocol (251/00/02 – corrections via Note to File)	